PSJ2 Exh 41

Managing Chronic Pain and the Importance of Customizing Opioid Treatment

KADIAN®
Morphine Sulfate Extended-Release Capsules
10mg • 20mg • 30mg • 50mg • 60mg • 80mg • 100mg • 200mg

Program Objectives

- To discuss pragmatic issues involved in managing chronic pain with opioid medications
- To review importance of customized therapy for patients with chronic pain, emphasizing opioid treatment

KADIAN® capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, “around-the-clock” opioid analgesic is needed for an extended period of time. KADIAN® capsules are not for use as an as-needed (prn) analgesic.

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Program Objectives
Key points
The goals of this program are to have an interactive discussion of the pragmatic issues involved in managing chronic pain with opioid medications and in particular, to illustrate the importance of customized therapy for patients with moderate to severe chronic pain

Supplemental note
KADIAN® capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, "around-the-clock" opioid analgesic is needed for an extended period of time. KADIAN® capsules are not for use as an as-needed (prn) analgesic

Chronic Pain Is Undertreated

- The undertreatment of chronic pain is a serious public health issue that results in enormous social cost and reduces patients' functional status and quality of life[1,2]
  - > Approximately 35% of adults suffer from chronic pain; ~11% live with severe chronic pain[3]
- Pain control, including behavioral and exercise programs, as well as medical therapy, can improve patients' emotional well-being and quality of life[1,4]

1. American Academy of Pain Medicine and the American Pain Society Consensus Statement. 1997:1-3.
2. Federation of State Medical Boards of the United States, Inc. Model policy for the use of controlled substances for the treatment of pain. 2004:1-5. 3. IASP. *Pain: Clinical Updates*. 2003;11:1-4. 4. APS. Chronic pain in America: roadblocks to relief. 1999.

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Chronic Pain Is Undertreated

Key point

Pain is among the most common reasons for seeking medical attention.1 Yet, the undertreatment of pain is a serious health concern that results in enormous social cost and reduces patients' functional status and quality of life2

Supplemental notes

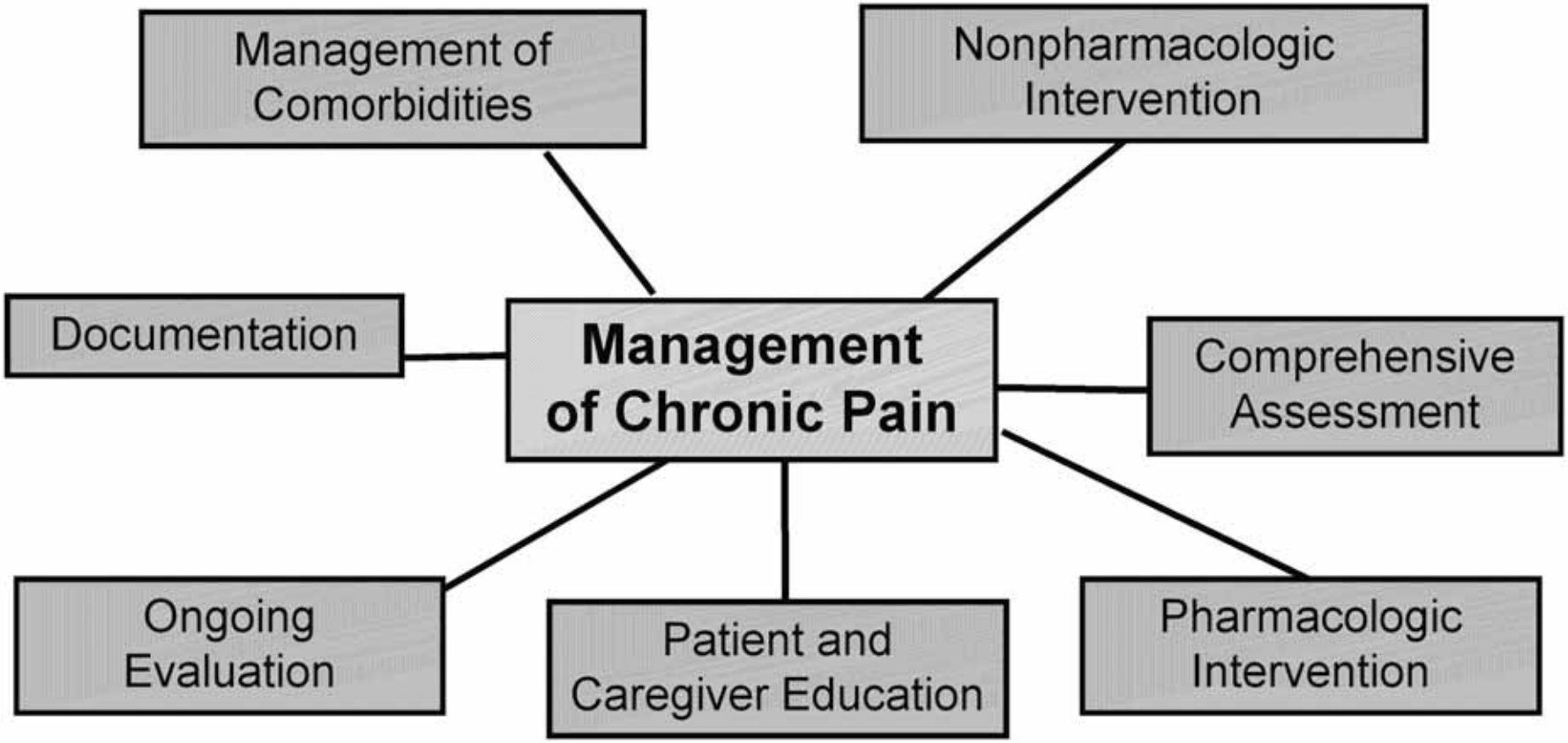
According to the International Association for the Study of Pain, the prevalence of chronic pain among adults is 35% and approximately 11% of adults in the general population experience severe chronic pain3

Pain management approaches may include behavioral and rehabilitative programs, as well as pharmacologic therapies, and may improve patients' sense of well-being and quality of life1

References for notes

1. American Academy of Pain Medicine and the American Pain Society Consensus Statement. The use of opioids for the treatment of chronic pain. 1997:1-3.
2. Federation of State Medical Boards of the United States, Inc. Model policy for the use of controlled substances for the treatment of pain. 2004:1-5.
3. International Association for the Study of Pain. How prevalent is chronic pain? Pain: Clinical Updates. 2003;11:1-4.

Components of Chronic Pain Management[1,2]



1. AGS Panel on Persistent Pain in Older Persons. *J Am Geriatr Soc.* 2002;50:S205-S224. 2. Federation of State Medical Boards of the United States, Inc. Model policy for the use of controlled substances for the treatment of pain. 2004:1-5.

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Components of Chronic Pain Management
Key point
Pharmacotherapy is one aspect of pain management; analgesic medication is a vital and common treatment method to control pain1

Supplemental notes
A comprehensive assessment includes a complete medical history, physical examination, pain assessment, psychological assessment, and an assessment of cognitive function1
Proper/adequate documentation includes obtaining informed consent and agreement for treatment, keeping accurate and complete medical records, and possessing evidence of compliance with laws and regulations for using controlled substances2

References for notes
American Geriatrics Society Panel on Persistent Pain in Older Persons. The management of persistent pain in older persons. J Am Geriatr Soc. 2002;50:S205-S224.
Federation of State Medical Boards of the United States, Inc. Model policy for the use of controlled substances for the treatment of pain. 2004:1-5.

What Is the Role of Long-Acting Opioid Therapy in the Treatment of Chronic Pain?

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Long-Acting Opioid Therapy for Chronic Pain

- Opioids are an essential part of a pain management plan for many patients[1]
- Treatment goals include reducing daily pain levels and improving the patient's functional ability[2]
- Opioids can be used with minimal risk in chronic pain patients without a history of abuse or addiction[3]
- Longer-acting agents are more effective than short-acting agents for chronic pain; "around-the-clock" dosing for "around-the-clock" pain[4]

1. American Academy of Pain Medicine and the American Pain Society Consensus Statement. 1997:1-4. 2. Marcus DA. *Am Fam Physician*. 2000;61:1331-1338. 3. National Cancer Institute. Substance abuse issues in cancer (PDQ®) health professional version. NCI Website; 2004. Accessed December 13, 2006. 4. Veterans Affairs, US Department of Defense. The management of opioid therapy for chronic pain. 2003;1-54.

Opioid Therapy for Chronic Pain

Key points

Opioids are considered to be an important part of the pain management plan for many patients.1 Maintenance therapy with these agents can be safer than the long-term use of other analgesics, such as cyclooxygenase type 2 (COX-2) inhibitors, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen2

References for notes

American Academy of Pain Medicine and the American Pain Society Consensus Statement. The use of opioids for the treatment of chronic pain. 1997:1-4.

American Geriatrics Society Panel on Persistent Pain in Older Persons. The management of persistent pain in older persons. J Am Geriatr Soc. 2002;50:S205-S224.

Opioids Can Be a Safer Option Than Other Analgesics

- Maintenance therapy with opioids can be safer than the long-term use of other analgesics, such as COX-2 inhibitors, nonselective NSAIDs, or acetaminophen, in older persons[1]
  - Acetaminophen toxicity is a major health concern; the upper limit, as stated by the American Pain Society, is only 4000 mg, which can be attained through only a few doses of short-acting opioids[2]
  - 4000 mg of acetaminophen can cause significant elevations in hepatic enzyme (ALT) levels in as little as 2 weeks[3]
  - Acetaminophen poisoning is the most common cause of acute liver failure in the USA and the UK[4]

1. AGS Panel on Persistent Pain in Older Persons. *J Am Geriatr Soc*. 2002;50:S205-S224. 2. American Pain Society. *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain*. 5th ed. Glenview, IL: American Pain Society; 2003:9-11. 3. Watkins P, Kaplowitz N, Slattery J, Colonese C, Colucci S, Stewart P, Harris S. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily. *JAMA*. 2006;296(1):8793. 4. Larson A, Polson J, Fontana R, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology*. 2005;42(6):1364-1372.

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Opioid Therapy for Chronic Pain

Key points

Opioids are considered to be an important part of the pain management plan for many patients.1 Maintenance therapy with these agents can be safer than the long-term use of other analgesics, such as COX-2 inhibitors, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen2

Acetaminophen toxicity can be reached in only 4000 mg, causing elevations in hepatic ALT levels and acute liver failure2-4

References for notes

American Academy of Pain Medicine and the American Pain Society Consensus Statement. The use of opioids for the treatment of chronic pain. 1997:1-4.

American Pain Society. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 5th ed. Glenview, IL: American Pain Society; 2003:9-11.

Watkins P, Kaplowitz N, Slattery J, Colonese C, Colucci S, Stewart P, Harris S. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily. JAMA 2006;296(1):8793.

Larson A, Polson J, Fontana R, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology. 2005;42(6):1364-1372.

Universal Precautions in Pain Medicine

1. Psychological assessment, including risk of addictive disorders
2. Informed consent
3. Treatment agreement
4. Pre-/post-intervention assessment of pain level and function
5. Appropriate trial of opioid therapy + / − adjunctive medication
6. Reassessment of pain score and level of function
7. Regularly assess the four “A’s” of pain medicine
   Analgesia, Activity, Adverse effects, Aberrant behavior
8. Periodically review pain diagnosis and comorbid conditions, including addictive disorders
9. Documentation

Gourlay DL et al. *Pain Med*. 2005;6:107-112.

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Universal Precautions in Pain Medicine

Key point

Because uncertainty may exist regarding the misuse, abuse, or diversion of opioid analgesics, all patients should be treated according to the Universal Precautions in Pain Medicine

Reference for notes

Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. Pain Med. 2005;6:107-112.

Why Should Individualized Treatment Be Considered, and What Is the Role of Long-Acting Opioids?

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Individualization of Treatment

Opioid responsiveness is highly variable and cannot be reliably predicted in individual patients[1,2]

Keys to individualization of opioid therapy may include:

- Having a working knowledge of available agents[2]
- Start low and titrate until patient reports adequate analgesia[1,3]
- Set dose levels on basis of patient need, not on predetermined maximal dose[3]
- Frequently monitor patients for treatment effect and adverse events[3]
- Assess and document adherence with appropriate use of opioids

1. AGS Panel on Persistent Pain in Older Persons. *J Am Geriatr Soc.* 2002;50:S205-S224. 2. Nicholson B. *Drugs.* 2003;63:17-32. 3. Veterans Affairs, US Department of Defense. The management of opioid therapy for chronic pain. 2003;i-54.

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Individualization of Treatment

Key point

Individual response to opioid therapy is highly variable.1 Therefore, it is important to individualize opioid analgesic regimens to minimize side effects and to maximize response2

References for notes

AGS Panel on Persistent Pain in Older Persons. J Am Geriatr Soc. 2002;50:S205-S224.
Nicholson B. Responsible prescribing of opioids for the management of chronic pain. Drugs. 2003;63:17-32.
Mercadante S. World Health Organization guidelines—problem areas in cancer pain management. Cancer Control. 1999;6:191-197.

Currently Available Long-Acting Opioids

	Dosing Interval	Available Strengths	Administration	IR Component	Ceiling Dose
KADIAN®	q12hr q24hr	10, 20, 30, 50, 60, 80, 100, 200 mg	Capsule, Sprinkle, G-Tube	No	–
AVINZA®	q24hr	30, 60, 90, 120 mg	Capsule, Sprinkle	Yes	1600 mg/day
OxyContin®	q12hr	10, 20, 40, 80, 160 mg	Tablet	Yes	–
MS Contin®	q8hr q12hr	15, 30, 60, 100, 200 mg	Tablet	No	–
Opana® ER	q12hr	5, 10, 20, 40 mg	Tablet	No	–
Oramorph® SR	q12	15, 30, 60, 100 mg	Tablet	No	–
Duragesic®	q72hr	12, 25, 50, 75, 100 mcg/hr	Transdermal Patch	No	–

IR = immediate-release.

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Currently Available Long-Acting Opioids

Key points

Currently, there are a number of branded long-acting opioids with US Food and Drug Administration indications for moderate to severe chronic pain. In addition, OxyContin®, MS Contin®, and Duragesic® have generic equivalents. There are no generic equivalents for KADIAN®, AVINZA®, or OPANA® ER

This grid compares several key characteristic features of available long-acting opioid analgesics

As shown here, KADIAN® can be given as either q24h or q12h, has 8 dosage strengths, 3 different administration methods, no immediate-release (IR) component, and no maximum recommended dose1

Supplemental notes

The IR component for AVINZA® is 10% of dose; the ceiling dose is 1600 mg/day because of the presence of fumaric acid2

The IR component of OxyContin® is 38% to 40%3

References for notes

KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC.

AVINZA® [package insert]. Bristol, TN: King Pharmaceuticals, Inc.; 2007.

Mandema JW, Kaiko RF, Oshlack B, Reder RF, Stanski DR. Characterization and validation of a pharmacokinetic model for controlled-release oxycodone. Br J Clin Pharmacol 1996;42:747-756.

Morphine Is the Benchmark Analgesic

- The gold standard in pain control—reliable, with proven efficacy and safety when taken appropriately[1-4]
- Improves quality of life for patients, helping to maintain daily activity, independence, mental awareness, and dignity[4]
- Appropriate for both malignant and nonmalignant chronic pain[5]
- No ceiling dose or acetaminophen toxicity[6]

1. American Pain Society. *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain.* 5th ed. Glenview, IL: American Pain Society; 2003. 2. Oxford Textbook of Palliative Medicine. 2nd ed. Doyle D, Hanks GWC, MacDonald N, eds. Oxford, England: Oxford University Press; 1998. 3. Labby D, Koder M, Amann T for Oregon Health and Science University. *Opioids and Chronic Non-malignant Pain: A Clinicians' Handbook.* Oregon Health and Science University. Portland, OR. Available at: http://www.ohsu.edu/ahec/pain/appendixB.pdf. Accessed February 13, 2008. 4. Red River Valley Group. *Myths about morphine.* Hospice of Red River Valley Newsletter. Volume 11, Issue. 5. Available at: http://www.hrrv.org/pdf/DT1203.pdf. Accessed February 13, 2008. 5. American Pain Society. *Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis.* 2nd ed. Glenview, IL: American Pain Society; 2002. 6. KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC.

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Morphine Is the Benchmark Analgesic

Key points

Morphine is a well-tolerated, highly effective opioid that has been used in a variety of therapeutic settings for many decades

KADIAN® Capsules: Customizing Chronic Pain Management With a Long-Acting Morphine

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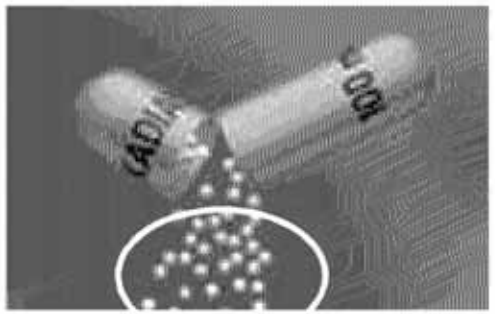
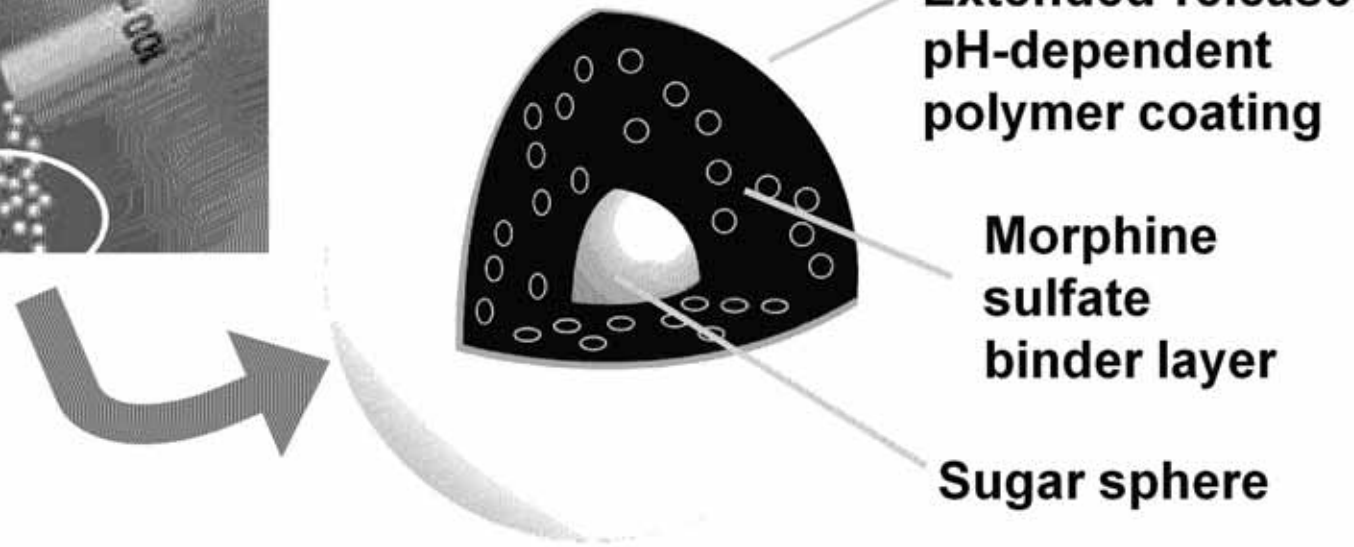
KADIAN® (morphine sulfate extended-release) Capsules/Pellet Technology

- Multiple pellets are enclosed in a gelatin capsule
- Innovative polymer-coated pellet technology
- KADIAN® formulation provides no immediate-release component





Gourlay GK. *Clin Pharmacokinet*. 1998;35:173-190.

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KADIAN® (morphine sulfate extended-release) Capsule/Pellet Technology

Key point

The pellets in KADIAN® capsules are designed to slowly release morphine sulfate over an extended period of time and provide analgesia for up to 24 hours1

Supplemental notes

KADIAN® pellets are composed of a sugar core surrounded by a morphine-containing layer. The outermost layer is a polymer coat2

After ingestion, the capsule's gelatin coat dissolves and morphine pellets are released

In the stomach, some components of the shell dissolve, forming pores through which morphine may diffuse outwardly; these pores are relatively small, allowing only a limited diffusion of morphine

As the pellets move through the gastrointestinal tract, additional components dissolve, forming larger pores and releasing greater amounts of morphine

KADIAN® capsules are gluten-free1

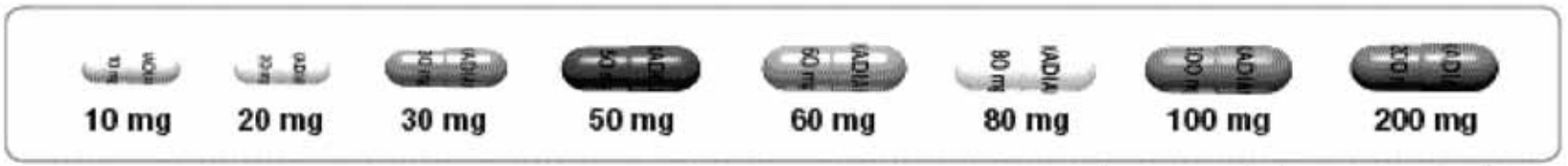
References for notes

KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC.

Gourlay GK. Sustained relief of chronic pain: pharmacokinetics of sustained release morphine. Clin Pharmacokinet. 1998;35:173-190.

Unique Dosing Flexibility With KADIAN®

- Extended-release capsule formulation allows for administration q24h or q12h
- 8 different dosage strengths available
  - > 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, and 200 mg capsules
  - > Capsule combinations facilitate titration in 10 mg increments
- No ceiling dose, does not contain acetaminophen
- 3 modes of administration
  - > Capsules, sprinkle option, and (G)-tube dosing*
- No significant food effect



Capsules are not shown at actual size.

*The administration of KADIAN® pellets through a nasogastric tube should not be attempted.

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Individualized Dosing With KADIAN®

Key point

KADIAN® possesses several key features that assist in tailoring pain therapy for the individual patient

KADIAN® is available in 8 different dosage strengths, allowing titration in 10 mg increments to achieve an appropriate individual balance between analgesia and opioid side effects1

KADIAN® has no maximum recommended dose (ceiling dose), because KADIAN® does not contain acetaminophen, ibuprofen, or fumaric acid1

KADIAN® achieves comparative bioavailability during fed and fasted states without regard to whether capsules are swallowed whole or administered as pellets in apple sauce1

Supplemental notes

High doses of acetaminophen may lead to hepatic toxicity

Ibuprofen use may lead to gastrointestinal adverse events

AVINZA®, which is also an extended-release formulation of morphine sulfate, is labeled for a maximum dosage of 1600 mg/day. The formulation of AVINZA® contains fumaric acid. Fumaric acid is a common component of food additives, oral medicines, and dietary supplements and it is therefore difficult to ascertain the amount of fumaric acid being ingested. Fumaric acid has not been demonstrated to be safe at large doses, and may be associated with serious renal toxicity2

References for notes

KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC.

AVINZA® [package insert]. Bristol, TN: King Pharmaceuticals, Inc; 2007.

Initiating KADIAN® Therapy

- For opioid-naive patients
  - Patients who do not have a proven tolerance to opioids should be started on 10 or 20 mg strength
- Conversion from other oral morphine formulations to KADIAN®
  - KADIAN® should be started by administering the total daily oral morphine dose q24h (once-a-day) or by administering one-half of the total daily oral morphine dose q12h (twice-a-day)
  - If breakthrough pain occurs, the dose may be supplemented with a small dose (<20% of the total daily dose) of a short-acting analgesic
  - The dose should be titrated no more frequently than every-other-day to allow patients to stabilize before escalating the dose
- Conversion from other oral opioids to KADIAN®
  - In general, it is safest to give half of the estimated daily morphine demand as the initial dose

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Initiating KADIAN® Therapy

Key point

When initiating KADIAN® therapy, a number of factors should be considered

Supplemental notes

The optimal use of opioid analgesics in the management of chronic malignant and nonmalignant pain is challenging, and is well described in materials published by the World Health Organization and the Agency for Health Care Policy and Research, which are available from Alpharma upon request. KADIAN® is a third-step drug, which is most useful when the patient requires a constant level of opioid analgesia as a "floor" or "platform" from which to manage breakthrough pain. When a patient has reached the point where comfort cannot be provided with a combination of nonopioid medications (NSAIDs and acetaminophen) and intermittent use of moderate or strong opioids, the patient's total opioid therapy should be converted into a 24-hour oral morphine equivalent1

Tolerance is the phenomenon whereby chronic exposure to a drug diminishes its antinociceptive or analgesic effect or creates the need for a higher dose to maintain this effect.2 Cross-tolerance, therefore, describes the observation that tolerance to one drug confers tolerance to another.3 However, during the conversion of one opioid to another opioid, the cross-tolerance is not complete (incomplete) or dose-equivalent, which may be accounted for by different mechanisms of action. Therefore, given this potential variability during conversion, a conservative, safer approach has been suggested to decrease the dose-equivalent amount of opioid by 25% to 50% of the new drug. These measures are based on clinical experience and not empiric evidence4

Depending on patient needs and the clinical situation, it may be appropriate to use an equivalent analgesia conversion ratio

Some patients may be accustomed to feeling euphoria with IR components of many other long-acting analgesics. Some practitioners choose to slowly convert patients from their previous opioid analgesic by gradually decreasing the dose of previous therapy while concurrently initiating the new analgesic at lower doses, and increasing according to patients' needs

References for notes

KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC.

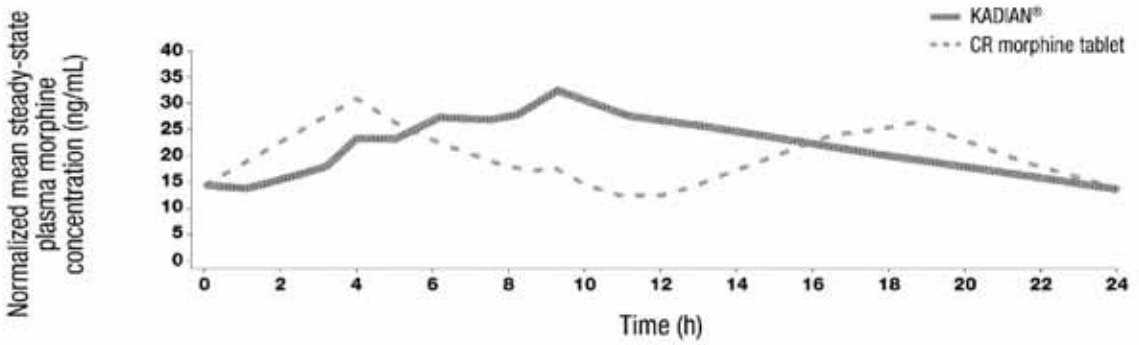
International Association for the Study of Pain. Analgesic tolerance to opioids. Pain: Clinical Updates. 2001;9:1-8.

Adriaensen H. Opioid tolerance and dependence: an inevitable consequence of chronic treatment? Acta Anaesthesiol Belg. 2003;54:37-47.

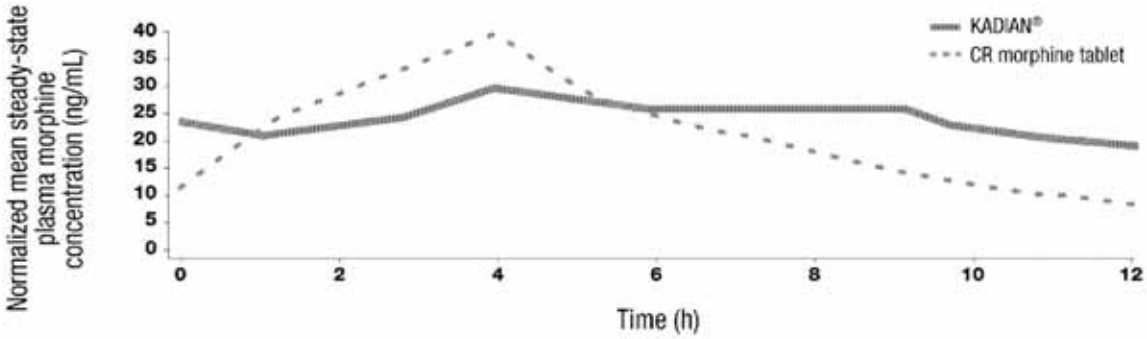
National Cancer Institute. Pain (PDQ®)—Health Professional Version. Bethesda, Md: US National Institutes of Health; last modified March 21, 2006.

KADIAN® Pharmacokinetics: Mean Steady-State Plasma Morphine Concentration

Pharmacokinetics of ONCE-DAILY KADIAN® vs twice-daily CR morphine tablets over 24 hours[1,2]



Pharmacokinetics of TWICE-DAILY KADIAN® vs twice-daily CR morphine tablets over 12 hours[1,2]



Randomized, double-blind, double-dummy, 2-way crossover studies with a lead-in period. Serum concentrations at steady state were normalized to 100 mg every 24 hours.

1. KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC. 2. Gourlay GK et al. *Pain*. 1997;69:295-302.

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Mean Steady-State Plasma Morphine Concentration

Key point

KADIAN® provides relatively level plasma concentrations over the dosing interval, whether administered q12h or q24h1,2

Supplemental notes

These graphs illustrate the mean concentration versus time profiles for KADIAN® q24h (graph on left side) and q12h (graph on right side) versus controlled-release morphine tablets q12h

Top graph: Tmax was significantly longer for KADIAN® versus controlled-release morphine tablets. While Cmax values were not significantly different between KADIAN® q24h and controlled-release morphine tablets q12h, Cmin values were significantly higher for KADIAN® compared with controlled-release morphine tablets, resulting in less fluctuation in plasma morphine concentration with KADIAN® throughout the dosing interval1,2

Bottom graph: Cmax values were significantly lower, and Cmin values were significantly higher for KADIAN® q12h compared with controlled-release morphine tablets q12h, resulting in less fluctuation in plasma morphine concentration with KADIAN® throughout the dosing interval1

Fluctuations in plasma morphine concentration for individual patients may be associated with breakthrough pain and/or side effects secondary to peaks (Cmax) and valleys (Cmin) in circulating drug levels

References for notes

KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC.

Gourlay GK, Cherry DA, Onley MM, et al. Pharmacokinetics and pharmacodynamics of twenty-four-hourly Kapanol compared to twelve-hourly MS Contin in the treatment of severe cancer pain. Pain. 1997;69:295-302.

The Importance of Steady Plasma Morphine Levels

- When plasma morphine concentrations drop, patients may feel more pain, and require rescue medication[1]
- Plasma morphine levels fluctuate less with KADIAN capsules than with CR morphine tablets[2]
- Longer-acting agents are more effective than short-acting agents for chronic pain; "around-the-clock" dosing for "around-the-clock" pain[3]
- Maintenance therapy with opioids can be safer than the long-term use of other analgesics, such as COX-2 inhibitors, nonselective NSAIDs, or acetaminophen, in older persons[4]

1. Gourlay GK, Cherry DA, Onley MM, et al. Pharmacokinetics and pharmacodynamics of twenty-four-hourly Kapanol compared to twelve-hourly MS Contin in the treatment of severe cancer pain. *Pain*. 1997; 69(3):295-302. 2. KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC. 3. Veterans Affairs, US Department of Defense. *The management of opioid therapy for chronic pain*. 2003;1-54. 4. AGS Panel on Persistent Pain in Older Persons. *J Am Geriatr Soc*. 2002;50:S205-S224.

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The Importance of Steady Plasma Morphine Levels

Key points

Steady plasma concentrations are desired when prescribing opioids, as fluctuating concentrations lead to incidents of breakthrough pain that require rescue medication1

Long-acting opioids posses more consistent steady-state plasma morphine levels than short-acting opioids2

References for notes

Gourlay GK, Cherry DA, Onley MM, et al. Pharmacokinetics and pharmacodynamics of twenty-four-hourly Kapanol compared to twelve-hourly MS Contin in the treatment of severe cancer pain. Pain. 1997; 69(3):295-302.

Veterans Affairs, US Department of Defense. The management of opioid therapy for chronic pain. 2003;1-54.

KRONUS-MSP Study

Kadian: **R**esponse **O**f **N**on-malignant, **U**nder-treated **S**ubjects with **M**oderate/**S**evere **P**ain—a 4-week prospective, randomized, open-label, blinded endpoint study

- 1428 adults with chronic, moderate to severe, nonmalignant pain with visual numeric scale (VNS) scores ≥4 (0=no pain; 10=worst pain)[1,2]
- Patients randomized to receive KADIAN® capsules once daily either in the am or pm for a 4-week treatment period[2]
- Dose increases were allowed in weeks 1 and 2; however, switching to q12h dosing was reserved until week 2; median total daily dose was 40 mg and titrated to a median dose of 50 mg/day at week 2, then to a median dose of 80 mg/day by week 4[1]
- All patients who took at least 1 dose of KADIAN® were included in the safety analysis (safety population); all patients in the safety population who had at least 1 valid baseline and post-baseline assessment were included in the efficacy analysis (intent-to-treat [ITT] population)[2]

1. Nicholson B, Ross E, Weil A, Sasaki J, Sacks G. Treatment of chronic moderate-to-severe non-malignant pain with polymer-coated extended release morphine sulfate capsules. *Curr Med Res Opin*. 2006;22(3):539-550. 2. Weil A, Nicholson B, Ross E, Sasaki J. Patients with chronic, non-malignant, moderate/severe pain can be successfully switched from other sustained-release morphine or oxycodone compounds to KADIAN® (morphine sulfate sustained-release capsules): the KRONUS-MSP trial. Poster presented at: American Pain Society 23rd Annual Scientific Meeting; May 6-9, 2004; Vancouver, BC, Canada.

KADIAN®
Morphine Sulfate Extended-Release Capsules
10mg · 20mg · 30mg · 50mg · 60mg · 80mg · 100mg · 200mg

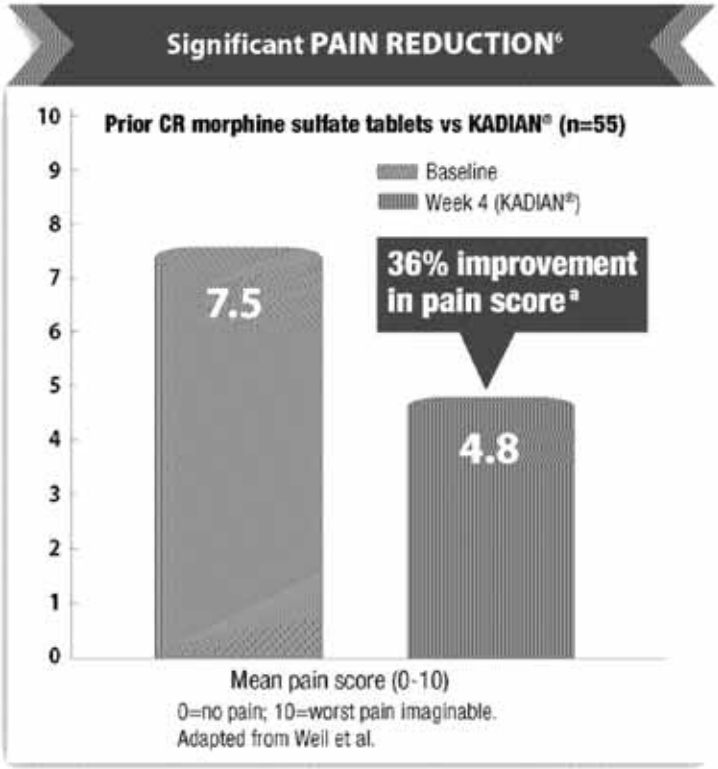
Key Points

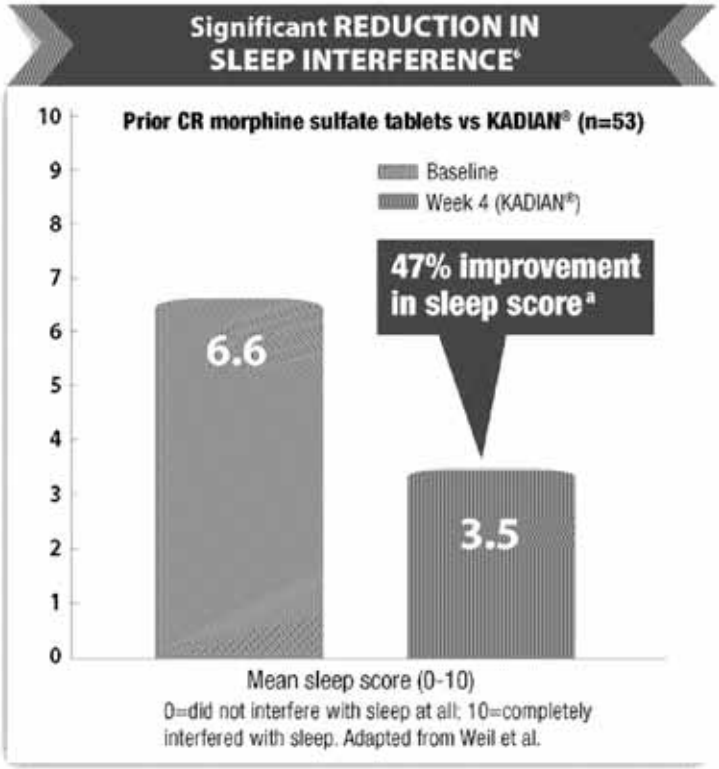
Highly significant improvements were shown with KADIAN® in all efficacy outcome measurements

KADIAN® was well tolerated

- Most frequently reported adverse events (AEs) were constipation (11.6%); nausea (9.2%); and somnolence (3.0%)
- 9.6% discontinued as a result of an adverse event

Improvements in Patients with Chronic Back Pain Using KADIAN®





Subanalysis of a randomized, open-label, blinded endpoint study of patients previously taking CR morphine tablets and switched to KADIAN®. Data extrapolated from subcut of substudy of 205 patients who were previously treated unsuccessfully with OxyContin or MS Contin.

a. Both significant at $P<0.001$. Baseline vs week 4 per protocol population, post hoc analysis.

Weil A, Nicholson B, Ross E, Sasaki J. Patients with chronic, non-malignant, moderate/severe pain can be successfully switched from other sustained-release morphine or oxycodone compounds to KADIAN® (morphine sulfate sustained-release capsules): the KRONUS-MSP trial. Poster presented at: American Pain Society 23rd Annual Scientific Meeting; May 6-9, 2004; Vancouver, BC, Canada.

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Improvements in Patients with Chronic Back Pain Using KADIAN®

Key points

Data are from a subanalysis of the KRONUS-MSP study, the largest study to date (N=1428) assessing the use of an extended-release opioid in the treatment of chronic, moderate to severe, nonmalignant pain in patients who reported inadequate analgesia with other opioid analgesics prior to entry in the study1,2

In a subcut of the subgroup of the KRONUS-MSP population, KADIAN® demonstrated a 36% improvement in pain score (Nn=55) and a 47% improvement in sleep score (n=53)2

As depicted in this figure, a statistically significant improvement in pain reduction and sleep from baseline to week 4 was also associated with KADIAN® treatment in this subgroup of study patients with moderate to severe chronic back pain3

Supplemental notes

Patient population: subgroup of patients from KRONUS-MSP (n = 205) with moderate to severe, nonspecific back pain (VNS pain score □4 out of 10)3

Assessments included VNS pain score and sleep quality based on patient scoring on a 10-point scale that the patient chose to best describe the degree to which pain interfered with sleep (0 = no sleep interference, 10 = completely interfered with sleep) at week 42

Median dose of KADIAN® in back pain population was 50 mg and 60 mg at baseline and week 2, respectively. Mean doses at baseline and week 2 were 59.4 mg, and 101.1 mg, respectively. Dosing frequency in back pain population: q24h = 57.2% and q12h = 42.8%4

References for notes

Nicholson B, Ross E, Weil A, Sasaki J, Sacks G. Treatment of chronic moderate-to-severe non-malignant pain with polymer-coated extended-release morphine sulfate capsules. Curr Med Res Opin. 2006;22:539-550.

Weil A, Nicholson B, Ross E, Sasaki J. Patients with chronic, non-malignant, moderate/severe pain can be successfully switched from other sustained-release morphine or oxycodone compounds to KADIAN® (morphine sulfate sustained-release capsules): the KRONUS-MSP trial. Poster presented at: American Pain Society 23rd Annual Scientific Meeting; May 6-9, 2004; Vancouver, BC, Canada.

Sasaki J, Weil A, Ross E, Nicholson B. Use of polymer-coated extended-release morphine sulfate in the treatment of chronic, non-malignant back pain. Poster presented at the 29th Annual Meeting of the Society of General Internal Medicine; April 26 – 29, 2006; Los Angeles, Calif.

Data on file. Alpharma Pharmaceuticals LLC, Piscataway, NJ.

Safety Considerations

Is KADIAN® a controlled substance?

- KADIAN® capsules contain morphine sulfate, an opioid agonist and a Schedule II controlled substance with an abuse liability similar to that of other opioid analgesics
  - This should be considered when prescribing or dispensing KADIAN® in situations where the prescriber or pharmacist is concerned about an increased risk of misuse, abuse, or diversion

Can KADIAN® be used with opioid-naive patients?

- Patients who do not have proven tolerance to opioids should be started on the 10 mg or 20 mg strength only
  - For those patients, doses are usually increased at a rate not greater than 20 mg every other day
  - KADIAN® 100 mg and 200 mg capsules are for use in opioid-tolerant patients only

KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC.

KADIAN®
Morphine Sulfate Extended-Release Capsules
10mg · 20mg · 30mg · 50mg · 60mg · 80mg · 100mg · 200mg

Safety Considerations

Key points

KADIAN® capsules contain morphine sulfate, an opioid agonist and a Schedule II controlled substance with an abuse liability similar to that of other opioid analgesics

This should be considered when prescribing or dispensing KADIAN® in situations where the prescriber or pharmacist is concerned about an increased risk misuse, abuse, or diversion

Patients who do not have proven tolerance to opioids should be started on the 10 mg or 20 mg strength only

For these patients, doses are usually increased at a rate not greater than 20 mg every other day

KADIAN® 100 mg and 200 mg capsules are for use in opioid-tolerant patients only

Reference for notes

KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC.

Safety Considerations (continued)

What are the serious adverse reactions that may be associated with KADIAN® use?

- Serious adverse reactions that may be associated with KADIAN® therapy include:
  - Respiratory depression
  - Respiratory arrest
  - Circulatory depression
  - Cardiac arrest
  - Hypotension
  - Shock
  - Apnea

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Safety Considerations (continued)
Key points
What are the serious adverse reactions that may be associated with KADIAN® use?
Serious adverse reactions that may be associated with KADIAN® therapy include:
Respiratory depression
Respiratory arrest
Circulatory depression
Cardiac arrest
Hypotension
Shock

Reference for notes

KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC.

Safety Considerations (continued)

What are the most commonly reported adverse events?*

Most commonly reported AEs in a clinical trial involving patients with moderate to severe, nonmalignant pain (n=1418)[1]

	Constipation	Nausea	Somnolence
KADIAN®	11.6%	9.2%	3.0%

Most commonly reported AEs in patients with chronic cancer pain in controlled clinical trials[2]

	Drowsiness	Constipation	Nausea	Dizziness	Anxiety
KADIAN®	9%	9%	7%	6%	6%

- Frequency of adverse events may be minimized by careful individualization of therapy and education regarding appropriate management of common adverse events

*Reported in ≥3% of patients.

1. Nicholson B, Ross E, Weil A, Sasaki J, Sacks G. Treatment of chronic moderate-to-severe non-malignant pain with polymer-coated extended-release morphine sulfate capsules. *Curr Med Res Opin*. 2006;22(3):539-550.
2. KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC.

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Safety Considerations (continued)

Key points

This slide presents the most common adverse events reported by ≥3% of patients in clinical trials who are experiencing either chronic cancer-related pain or moderate to severe nonmalignant pain

In many cases, the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dose, slow titration, and the avoidance of large swings in plasma concentrations of the opioid

Supplemental notes

The KADIAN® package insert also provides guidance on the management of several of these common adverse events:

Drowsiness: most patients receiving morphine will experience initial drowsiness that usually disappears within 3 to 5 days. The dosage should be adjusted according to individual needs

Constipation: virtually all patients experience constipation while taking opioids on a chronic basis. Patients must be cautioned accordingly, and laxatives, softeners, and other appropriate treatments should be used prophylactically from the beginning of opioid therapy

Nausea/vomiting: nausea/vomiting are common effects of opioid therapy; however, the frequency usually decreases within a week. Treatment with a suitable antiemetic or metoclopramide should be considered

Reference for notes

KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC.

Safety Considerations (continued)

How should KADIAN® be administered?

- KADIAN® capsules are to be swallowed whole, sprinkled on apple sauce or administered via G-tube and are not to be chewed, dissolved, or crushed. Taking chewed, dissolved, or crushed KADIAN® capsules or pellets leads to rapid release and absorption of a potentially fatal dose of morphine

Can patients drink alcoholic beverages while using KADIAN®?

- KADIAN® should not be taken with alcohol or other CNS depressants except by order of the prescribing healthcare provider because dangerous synergistic effects may occur resulting in respiratory depression, hypotension, and profound sedation, and coma

CNS = central nervous system.

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Safety Considerations (continued)

Key points

How should KADIAN® be administered?

KADIAN® capsules are to be swallowed whole, sprinkled on apple sauce, or administered via G-tube and are not to be chewed, dissolved, or crushed. Taking chewed, dissolved, or crushed KADIAN® capsules or pellets leads to rapid release and absorption of a potentially fatal dose of morphine

May patients drink alcoholic beverages while using KADIAN®?

KADIAN® should not be taken with alcohol or other CNS depressants except by order of the prescribing healthcare provider, because dangerous synergistic effects may occur resulting in serious injury or death

Reference for notes

KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC.

KADIAN® (morphine sulfate extended-release) Capsules

- KADIAN® is indicated for the management of moderate to severe pain when a continuous, "around-the-clock" opioid analgesic is needed for an extended period of time[1]
- Unique dosing flexibility
  - Flexible dosing schedules (q24h or q12h)
  - Flexible titration with 8 dosing strengths
- Smooth steady-state plasma levels can prevent breakthrough pain and reduce the need for rescue medication
- Proven efficacy and improvement in quality-of-life (QOL) sleep scores in patients with chronic back pain
- Demonstrated tolerability with no ceiling dose; contains no acetaminophen or fumaric acid

1. KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC.

KADIAN®
Morphine Sulfate Extended-Release Capsules
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KADIAN® (morphine sulfate extended-release) Capsules

Key points

KADIAN® is indicated for the management of moderate to severe pain when a continuous, "around-the-clock" opioid analgesic is needed for an extended period of time

Several key KADIAN® features offer patients the flexibility of customized pain therapy, including adjustable dosing schedules and routes of administration, and 8 dosage strengths for fine-tuned titration

KADIAN® has no ceiling dose and contains no fumaric acid, acetaminophen, or ibuprofen, allowing for easy titration to achieve an appropriate balance between analgesia and opioid side effects

Reference for notes

KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC.

Backup Slides

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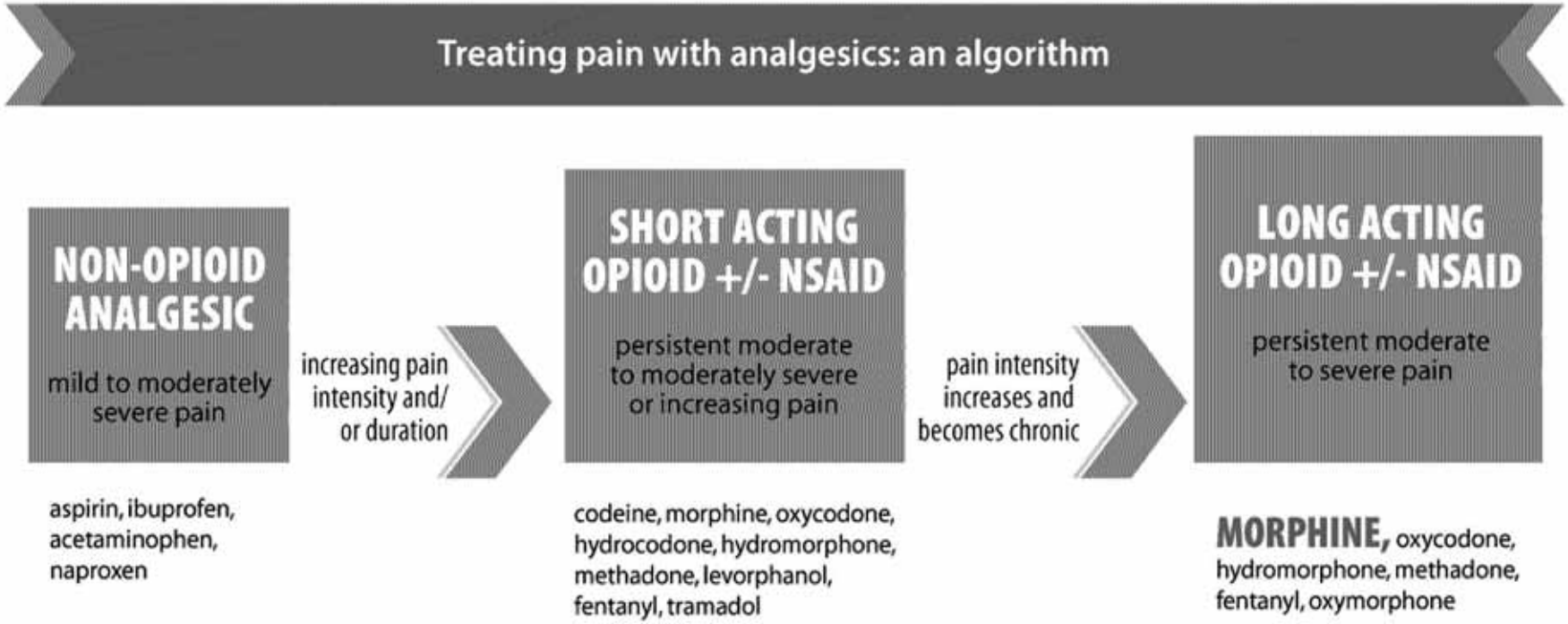
Backup slides

World Health Organization (WHO) Guidelines

WHO guidelines recommend treating chronic pain with a long-acting opioid



Adapted from WHO 3-step analgesic ladder

Oxford Textbook of Palliative Medicine. 2nd ed. Doyle D, Hanks GWC, MacDonald N, eds. Oxford, England: Oxford University Press; 1998.

KADIAN® Morphine Sulfate Extended-Release Capsules
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World Health Organization Treatment Guidelines
Key point
According to the World Health Organization's 3-step analgesic ladder, the use of opioids is suggested for patients with moderate and moderate to severe pain that is inadequately controlled with nonopioids (steps 2 and 3)1

References for notes
Mercadante S. World Health Organization guidelines—problem areas in cancer pain management.
Cancer Control. 1999;6:191-197.

KADIAN® (morphine sulfate extended-release) Capsules: Flexible Administration

Three modes of administration:

- Capsule for easy swallowing
- Sprinkle dosing
  - > Capsule contents can be opened and sprinkled on apple sauce for patients who have difficulty swallowing
- Gastrostomy (G)-tube dosing*
  - > Contents of capsule can also be sprinkled in water and administered through a 16 French or larger G-tube

*The administration of KADIAN® pellets through a nasogastric tube should not be attempted.

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KADIAN® capsules: Flexible Administration

Key point

KADIAN® offers the flexibility of 3 different methods of administration: capsule, sprinkling over apple sauce, or via a gastrostomy (G)-tube1

Supplemental notes

Individual patients, including those who have swallowing difficulties and those using a G-tube, may require alternate modes of administration1

Administration through a nasogastric tube should not be attempted1

Patients with chronic pain conditions often require long-term analgesia. Also, swallowing impairment in older persons is often a health care problem, especially among nursing home residents. Up to 60% of nursing home residents have signs of swallowing disorders or dysphagia.2 KADIAN® offers the flexibility for alternative methods of administration, which may be important for those patients

References for notes

KADIAN® Package Insert. Piscataway, NJ: Alpharma Pharmaceuticals LLC.

Smith TL, Sun MM, Pippin J. Research and professional briefs: characterizing process control of fluid viscosities in nursing homes. J Am Diet Assoc. 2004;104:969-971.